

SAMPLE INFORMED CONSENTS

Phase I Study of Fenretinide (4-HPR, NSC 374551) Lym-X-Sorb™(LXS) Oral Powder in Patients with Recurrent or Resistant Neuroblastoma

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

CONFLICT OF INTEREST DISCLOSURE

The Children's Hospital Los Angeles (CHLA) holds patents and/or patent applications on Fenretinide Lym-X-Sorb oral powder (the study drug). The inventors of Fenretinide Lym-X-Sorb oral powder, Drs. Barry Maurer and C. Patrick Reynolds (Texas Tech University Health Sciences Center, Lubbock, TX) and CHLA may potentially benefit financially from the development and future use of the study drug. If you have any questions regarding this disclosure, please contact the Conflict of Interest in Research Committee (COIRC) at CHLA (323-361-8368).

The word “you” used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial (a type of research study using human patients). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

You are being asked to participate in this study because you have been diagnosed with neuroblastoma, a type of solid cancer that usually affects children. Your cancer has either relapsed, or you have persistent tumor after having gotten standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To determine if the levels of fenretinide in the blood in patients given 2.2% fenretinide powder prepared in a special mixture of fats, sugar and wheat flour (called Lym-X-Sorb™ (LXS) oral powder) when it is given with any type of food that does not have high amounts of milk fat three times per day are different than the levels seen with the 3% fenretinide powder when it was given in SlimFast twice daily.
- To find a dose of a drug used for fungal infections, called ketoconazole, that can be given by mouth (orally) once each day, for 7 days, every 3 weeks, in combination with fenretinide without causing severe side effects.
- To find out the side effects seen by giving 2.2% 4-HPR/LXS oral powder with or without ketoconazole
- To measure blood levels of fenretinide during treatment with or without ketoconazole.
- To measure levels of fenretinide in normal white blood cells during treatment.
- To determine if your tumor gets smaller after treatment with 4-HPR/LXS oral powder with or without ketoconazole.
- To describe how many patients who agree to send bone marrow specimens for a special testing are found to have tumor cells by this new more sensitive test (called TLDA)

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

Fenretinide is an anticancer agent that may work differently than standard chemotherapy medicines. It may cause the buildup of a wax-like substance in neuroblastoma cancer cells, called "ceramide". In laboratory studies it was found that if too much ceramide builds up in neuroblastoma cells, they die.

Fenretinide has been given by mouth as a capsule to many people, including children. When Fenretinide is given in capsules, very little of the drug is absorbed through the intestines into the body. That meant that patients had to take many capsules of Fenretinide by mouth several times a day. In this study, a new oral preparation of fenretinide (called 4-HPR/LXS oral powder) is being tested to see if more fenretinide can be absorbed into the body. This is the first study of 4-HPR/LXS oral powder in either children or adults.

Thirty-two children with neuroblastoma have been treated with a 3% version of the fenretinide powder used on this study to date and approximately 20 patients with a 2.2% version of the fenretinide powder, and no toxicity occurred that limited the dosage. No serious or unexpected side effects occurred. However, the amount of drug found in the blood did not increase at the higher dosage levels, and so a dose of fenretinide lower than the highest one tested will be used for this part of the study.

Some children found it difficult to take the amount of drug prescribed when it was given twice each day, and so in this part of the study the total daily dose will be split into 3 doses per day. Some children also did not like taking the fenretinide in SlimFast, which was required in the first part of the study. In this part of the study, the drug may be taken in any food that does not have a high amount of milk fat.

We are also testing to see if a drug called ketoconazole, commonly used to treat fungus infections, can increase fenretinide levels in the body by interfering with the body's ability to break down fenretinide.

Ketoconazole will be given at the same time as the fenretinide to some patients on this part of the study. This is the first time that this combination has been tried in people.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 60 total pediatric patients will take part in this study and receive either a 2.2% fenretinide-by- weight oral powder alone or in combination with ketoconazole.

WHAT WILL HAPPEN TO ME ON THIS STUDY AND WHAT IS INVOLVED?

If you agree to be on this study, we will ask you to do the following things.

In the first nineteen patients treated, 4-HPR/LXS oral powder was mixed in foods or liquids that do not have a large amount of milk fat will be given by mouth three times a day, for 7 days, every three weeks. This did not seem to adversely affect how much fenretinide was absorbed into the body compared to giving the fenretinide powder mixed in SlimFast liquid nutritional shakes. You will take the fenretinide powder mixed into any room temperature or colder food or liquid/beverage you want, EXCEPT food or liquids that are high in milk fat. You can best decide how you like to take the drug powder. You can also mix in fruits or flavorings as long as they don't have large amounts of milk fats in them. This means you cannot use ice cream or whole or 2% milk. Milk fats may change the drug so it may not be the same. You will not need to be in the hospital to receive the drug. If you have bad side effects, you can continue treatment with a lower dose of 4-HPR/LXS oral powder, provided your side effects have gone away and your tumor is not getting worse.

All patients will get the same dose of 4-HPR/LXS oral powder that has already been shown to be tolerated without bad side effects in several children with neuroblastoma. Your dose will not change with later courses of treatment, unless it needs to be decreased due to side effects.

In the second group of twelve or so patients treated the same dose of fenretinide will be given, but will also take a common antifungal drug, called ketoconazole, along with the 4-HPR/LXS oral powder. We are testing to see if ketoconazole can further increase fenretinide levels in the body by slowing down the body's ability to get rid of fenretinide. If the dose of ketoconazole causes side effects, then a third group of patients will be treated at a lower dose of ketoconazole with the same dose of fenretinide as all other patients.

Your physician will let you know if you will receive fenretinide alone, or fenretinide in combination with ketoconazole.

Required Medical Tests

You will have a series of standard medical tests before, during, and following treatment with 4-HPR/LXS oral powder. Researchers will use these tests to measure the effectiveness of the treatment and what it is doing to your body.

Medical Tests Before and During Treatment

Physical exam	Tests of vision
Blood tests	Chest x-ray (only before treatment starts)
Pregnancy test	Bone marrow tests [#]
Urine tests	Various scans*
Tests of heart function	

[#]: Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

*: Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG scans. We will recommend scans specific for your case and we will answer your questions about these scans.

Medical Tests Following Treatment

Physical exam Bone marrow tests[#]
Blood tests Various scans*
Urine tests
Tests of heart function

The chart at the end of this form tells you when these tests need to be done. During the first week of treatment for every course: Physical exams, blood and urine tests will be done at least once a week, sometimes twice a week.

- Bone marrow tests and various scans will be done after the third and fifth courses, then after every four courses of treatment thereafter.

To prevent potential severe effects to the liver during this therapy: NO ACETAMINOPHEN (Tylenol®) or acetaminophen containing products may be taken beginning 24 hours before, during and for 48 hours after the seven day course of oral fenretinide . Your doctor will talk about other medicines that can be used instead of acetaminophen during this time. Additionally, the antibiotic Ceftriaxone (Rocephin®) may NOT be given 24 hours prior to, during, and for 24 hours after the end of seven day course of oral fenretinide. Your doctor will talk about other antibiotics that can be used instead of Ceftriaxone during this time if antibiotic therapy is needed.

Other Special Studies:

In addition to the routine studies listed above, we would like to do other studies while you are enrolled on the study. These tests are called "pharmacokinetic studies" (the level of the drug in your blood is measured) and "intracellular fenretinide studies" (in this case, measuring the amount of fenretinide that gets into your white blood cells). Each of these special studies is described in detail below.

Because one of the main reasons to do this study is to find out if more fenretinide can be delivered into the body by giving it in 4-HPR/LXS oral powder by mouth rather than in capsules or the levels increased by ketoconazole, "the pharmacokinetic" blood tests are REQUIRED for you to participate in the study and get treatment with 4-HPR/LXS oral powder.

However, while they are very helpful to us, the "intracellular fenretinide" studies are voluntary. You may choose NOT to participate in the "intracellular fenretinide" studies and can still get treated on this study with 4-HPR/LXS oral powder. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in the "intracellular fenretinide" studies.

The results of these studies (pharmacokinetic and "intracellular fenretinide") will not affect your treatment while enrolled on this study. The results will not be told to you or your doctor and will not become part of your medical record.

DETERMINING THE BLOOD LEVELS OF FENRETINIDE WHEN IT IS GIVEN IN 4-HPR/LXS ORAL POWDER (CALLED "PHARMACOKINETICS").

THIS TEST IS REQUIRED.

One of the main goals of this study is to determine what fenretinide levels are reached in the blood. We know how much drug gets into the blood when fenretinide is given by mouth using the 3% oral powder mixed in SlimFast and given in two doses each day. We are now trying to find out if we can keep the same levels of fenretinide in the blood by giving 2.2% 4-HPR/LXS oral powder with your choice of food or liquid (except for those high in milk fat) and split the dose into 3 doses per day. Then we want to find out if adding ketoconazole will further increase the amount of fenretinide in the blood.

To determine this, blood will be taken during the first, second, and sixth courses of treatment. During the first course, about a half teaspoon of blood (~2 ml) will be taken about ten times while you are getting 4-HPR/LXS oral powder (over 7 days), and then one more time after the drug is stopped. This allows us to see how much and how fast the fenretinide builds up in the blood, and how quickly it leaves the blood once the drug is stopped. During the second and sixth courses, a half teaspoon of blood will be taken 6 times: before you take the morning dose of 4-HPR/LXS oral powder and then at four and six hours after the morning dose on the first and last days of each treatment course. Researchers will compare how the body processes the Fenretinide in Courses 1, 2, and 6 to see if there are any differences. The total amount of blood drawn for drug level testing in Course 1 and Course 2 is about 34 ml over 4 weeks. About another 12 ml of blood is taken in Course 6. If your dose of fenretinide or ketoconazole is decreased due to side effects, or you receive more than six courses of treatment, we may ask to repeat the fenretinide levels an extra time (about 1/2 teaspoon of blood for each sample).

Some patients may be able to have these specimens drawn from their central line. Everyone else will need to have a separate IV placed in a vein to draw the blood samples. This IV will be taken out after all the blood samples have been drawn. Your doctor and nurse will talk with you about whether your central line can be used to draw the blood samples or if you will need a separate IV placed.

This part of the study is required. Deciding not to take part in this part of the study means you will not be able to get treatment with the study drug, 4-HPR/LXS oral powder.

**Determining Levels of Fenretinide in White Blood Cells (called “Intracellular fenretinide studies”).
This test is VOLUNTARY.**

To get some idea of how well the fenretinide in 4-HPR/LXS oral powder may get into tumor cells, we will measure how well it gets into normal white cells in the blood. If fenretinide in 4-HPR/LXS oral powder is taken up well by normal white blood cells, we believe that it will also be taken up well by tumor cells. During Course 2 of treatment, about 4 teaspoons (~22 ml) will be taken 2 times (before starting, and while taking the 4-HPR/LXS oral powder) to test normal white blood cells. Some patients may be able to have these specimens drawn from their central line. Everyone else will need to have these specimens drawn through a vein. We would only do this test if your body is big enough for us to take this much blood without a problem or if you consent to having these blood specimens taken from a vein if your central line cannot be used.

This extra study is voluntary. If you do not agree to have these samples taken, you can still receive 4-HPR/LXS oral powder as part of this trial.

Testing bone marrow for tumor cells:

Each time you have a bone marrow test done to check how your tumor is responding to the 4-HPR/LXS oral fenretinide, an extra teaspoon of bone marrow (approximately 5 cc) will be taken from the right and left sides to do a new test for tumor cells (called TLDA) which is more sensitive than the standard testing available. The significance of finding tumor using TLDA is not yet known. This test will not be done in real time and the results will not be given to your treating doctor, since it is not known yet how to use these results in deciding on what therapy to give you for your tumor. **This extra test is voluntary.** If you do not agree to have this extra bone marrow taken, you can still receive 4-HPR/LXS oral fenretinide as part of this trial.

HOW LONG WILL I BE ON THIS STUDY?

You can continue to 4-HPR/LXS oral powder every 21 days for a total of six courses as long as your neuroblastoma responds to the treatment or you do not have bad side effects from taking 4-HPR/LXS oral

powder. If your tumor is responding, and there is enough drug available, you may be able to receive more than six courses of therapy with the agreement of your treating doctor. Some patients will enter this study with no tumor seen on their radiology tests or in their bone marrow. For this group of patients only, therapy will stop after a total of 12 courses (about 9 months), even if your tumor has not come back and if you have not had any bad side effects. After you stop treatment with 4-HPR/LXS oral powder, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Evaluations for this study will continue unless your tumor gets worse or you start another treatment for your neuroblastoma. Researchers will continue to collection information about you for a lifetime. Information will be collected about whether you are still alive, whether you have developed any side effects from the treatment or any additional cancer. This information may be gotten from your oncologist or family doctor at regular intervals.

You can remove yourself from this study at any time. In addition, your doctor may remove you from this study at any time if he/she does not feel it is in your best medical interest to continue with treatment.

WHAT ARE THE RISKS OF THE STUDY?

This is a phase I study. A phase I study looks at how common and serious side effects can be for each patient at each specific dose of drug. In this study, researchers will be looking at side effects seen in patients taking 2.2% 4-HPR/LXS oral powder and 4-HPR/LXS oral powder in combination with an antifungal antibiotic, called ketoconazole. We know what side effects were seen in patients taking Fenretinide capsules by mouth and in patients taking either the 2.2% or 3% powdered fenretinide. However, because the 2.2% and 3% 4-HPR/LXS oral powders have only been given to about 45 children, there may be risks we do not know about.

The following side effects (toxicities) were seen in people who took Fenretinide capsules by mouth, who took 2.2% or 3% fenretinide-by-weight 4-HPR/LXS oral powder, or who received an intravenous (in the veins) fenretinide emulsion formulation in a different Phase I study:

Likely side effects seen in 21-100 out of every 100 children.

- Itching and dry skin
- Temporary night blindness (decreased ability to see in the dark)
- Dry mouth
- Increased sensitivity of the skin to sunlight

Less Likely side effects seen in 5-20 out of every 100 children.

- Rash and skin peeling
- Dry eyes
- Conjunctivitis or red eye
- Other visual changes
- Joint and muscle pain
- Headache
- Dizziness or lightheadedness
- Irritation of the liver seen in blood tests results of liver function.
- Protein or blood in the urine
- Higher levels of fats in the blood
- Nausea and vomiting
- Diarrhea
- Belly pain or cramping
- Heartburn
- Decrease in the number of red and white blood cells and platelets made in the bone marrow.
- Feeling tired as a result of low red blood cells in the blood.

- Infection as a result of the low number of white blood cells in the blood
- Higher blood levels of enzymes that help digestion (lipase and amylase).
- Irritation of the pancreas called pancreatitis. You can have belly pain, nausea, vomiting and higher blood levels of fat (triglycerides) and enzymes called lipase and amylase that help with digestion. Pancreatitis and high blood levels of fats were seen in adult patients with leukemia/lymphoma who are enrolled in a study using an intravenous fenretinide emulsion.

Rare side effects seen in less than 5 out of every 100 people

- Arthritis or joint swelling
- Increased pressure in the brain (Pseudotumor cerebri)
- Hot flashes or flushing
- Allergic reaction. An unexpected allergic reaction to 4-HPR/LXS oral powder could occur, and in severe cases could be life threatening.
- Increase of calcium in the blood.
- Low amount of a protein in your blood called albumin
- Low amount of a chemical called phosphorous in your blood
- Temporary decrease in the ability of the kidney to filter the blood.
- Buildup of fluid around the lung.
- Temporary increase of pressure within the blood vessels of the lung.
- Bleeding as a result of low platelets.
- It is possible that your liver could be damaged which, in severe cases, could be life threatening.
- Death : There was one patient treated on the IV fenretinide study who died from liver failure after receiving the first course of fenretinide.

There was one death caused by liver failure at the highest dose of IV fenretinide tested in the current NANT study, among the 15 patients treated initially at four different doses of fenretinide. There were no other deaths among the other 14 pediatric patients related to the IV fenretinide drug. Patients treated after this event on the IV Fenretinide study will receive lower doses of IV fenretinide.

There can also be side effects from taking ketoconazole. Normally, these side effects only happen to people taking ketoconazole every day for long periods of time (weeks to months). However, we do not know what the side effects may be from taking ketoconazole with fenretinide.

Side effects that can occur with ketoconazole by itself include:

Less Likely side effects seen in 5-20 out of every 100 persons.

- Nausea
- Vomiting
- Irritation of the liver

Rare side effects seen in less than 5 out of every 100 persons.

- Pruritus (itching)
- Allergic Reaction, including very bad reactions
- Sensitivity to light
- Arthralgias (joint pain)
- Headache
- Vertigo (dizziness/lightheadedness)
- Somnolence (Sleepiness)
- Nervousness
- Insomnia (sleeplessness)

- Strange dreams
- Paresthesias (numbness and tingling)
- Depression (feeling “down”)
- Tinnitus (ringing noise of the ears)
- Increased pressure in the brain
- Decreased cholesterol in the blood
- Diarrhea (loose stools)
- Abdominal pain or cramping
- Constipation (hard stools)
- Flatulence (farting)
- Bleeding in the stomach
- Adrenal Insufficiency (low amounts of certain important hormones in the blood)
- Fever and Chills
- Hair loss
- Sweating
- Low white cells in the blood
- Low platelets in the blood
- Hemolytic anemia (breaking apart of the red blood cells in the blood)

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drug used in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them.

Risks starting from starting an IV and taking blood samples: The risks from starting an IV or having your blood taken are minimal but can cause pain and result in an infection or a blood clot. Experienced doctors or nurses will start the IV if needed and perform these blood draws to minimize this risk.

Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many of the side effects above went away shortly after the oral fenretinide capsules were stopped, but it is always possible that side effects may be long lasting or permanent. Some side effects may be life threatening and it is possible that death could occur as a rare side effect following treatment with 4-HPR/LXS oral powder. Patients are watched carefully and treatment will be stopped if bad side effects develop.

If you are taking Fenretinide and Ketaconazole together: to prevent potential severe effects to the liver during this therapy: NO ACETAMINOPHEN (Tylenol®) or acetaminophen containing products may be taken beginning 24 hours before, during and for 48 hours after the seven day Fenretinide course. Your doctor will talk about other medicines that can be used instead of acetaminophen during this time. Additionally, the antibiotic Ceftriaxone (Rocephin®) may NOT be given 24 hours prior to, during, and for 24 hours after the end of the seven day Fenretinide course. Your doctor will talk about other antibiotics that can be used instead of Ceftriaxone during this time if antibiotic therapy is needed.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Yes, there are other options for treatment. Instead of being in this study, you have these options:

- Treatment with chemotherapy medicines.
- Treatment with other experimental agents that may be available.
- No therapy at this time with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

You may read your record. The records are available to those people caring for you at this hospital. However, all efforts will be made to keep your information confidential. Unfortunately, we cannot guarantee absolute confidentiality. Information about you may be shared if required by law.

Organizations that may look at and/or copy your research records for quality assurance and data analysis include such groups as:

- New Approaches To Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you (your child) by a number.
- Independent auditor(s) monitoring quality assurance for the NANT Consortium
- The Investigational New Drug Sponsor (the supplier) of the 4-HPR/LXS oral powder, Dr. Barry J. Maurer, MD, PhD, Texas Tech University Health Sciences Center; The CHLA Committee on Clinical Investigations (CCI)
- The Federal Government – National Cancer Institute (NCI) and the Food and Drug Administration (FDA) may examine records of patients participating in this study.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The Children's Neuroblastoma Research Foundation and/or the Rapid Access to Interventional Development (RAID) program of the National Cancer Institute (NCI) through grants to Barry J. Maurer, MD PhD, of Texas Tech University Health Sciences Center as the Investigational New Agent (IND) sponsor will provide 4-HPR/LXS oral powder free of charge for this study. In this study, the 4-HPR/LXS oral powder is given by mouth by first mixing it in foods or beverages. You may need to purchase an antifungal antibiotic, called ketoconazole, which may or may not be covered by your insurance. Thus, you may need to purchase ketoconazole.

The pharmacokinetic studies, "intracellular fenretinide" blood tests , TLDA assay on bone marrow to detect tumor cells will be done at no cost to you if you agree to participate in this voluntary study. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw the blood from you for these tests.

If there is a problem getting 4-HPR/LXS oral powder fenretinide, your study doctor will talk with you about possible options. Taking part in this study may lead to added costs that may be covered by your insurance company. Please ask about any expected added costs or insurance problems.

getting 4-HPR/LXS oral powder fenretinide is being provided under a limited research grant. Therefore, a continuing supply of the drug cannot be guaranteed. If there is a problem getting the getting 4-HPR/LXS oral powder fenretinide, you would have to stop this therapy. Your study doctor would talk with you at that time about possible other options of therapy.

Taking part in this study may lead to added costs that may be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You and/or your insurance company will be charged for continuing medical care or hospitalization.

You will receive no payment for taking part in this study.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, carfare, parking, and baby sitter fees.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor _____ [*investigator's name(s)*]; if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment due to injury while being on the study.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [*name(s)*] at _____ [*telephone number*].

For questions about your rights while taking part in this study call the _____
[name of center] Institutional Review Board (a group of people who review research to protect your rights)
at _____ [telephone number].

WHERE CAN I GET MORE INFORMATION?

For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will also get a copy of this consent form. If you want more information about this study, please ask your study doctor.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at anytime.

CONSENTS FOR STUDIES FOR RESEARCH

#1 Blood Levels of fenretinide known as Pharmacokinetics

Researchers would like to take about half a teaspoon of blood (2 ml) a total of eleven times (10 times during and one time after) the first course of treatment with 4-HPR/LXS oral powder, and six times during the second and sixth courses of treatment. These are extra blood draws and if your central line cannot be used, you will need to have a separate IV started in a vein for these blood samples to be taken. The results of these tests will be confidential and not made available to you or your treating physician.

IF YOU DO NOT AGREE THAT THESE TESTS MAY BE PERFORMED, YOU MAY NOT PARTICIPATE IN THIS STUDY

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood collected for blood levels of fenretinide

_____ **NO**, I do not agree to have blood collected for blood levels of fenretinide. I understand that by refusing to let these blood samples be collected that I cannot participate in this study.

Signature: _____ **Date:** _____

#2 Blood Levels of fenretinide in normal white blood cells known as "intracellular fenretinide levels."

Researchers would like to take about 5 teaspoons (20 cc) of blood two times (just before the starting Course 2, and then again on Day 6) during the second course of 4-HPR/LXS oral powder. These are extra blood draws and if your central line cannot be used, you will need to have these specimens drawn

through a vein. The results of these tests will be confidential and not made available to you or your treating physician.

THESE TESTS ARE STRICTLY VOLUNTARY. YOU MAY STILL PARTICIPATE IN THE STUDY EVEN IF YOU DO NOT AGREE TO THESE TESTS.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood for fenretinide levels in normal white blood cells

_____ **NO**, I do not agree to have blood for fenretinide levels in normal white blood cells.

Signature: _____ **Date:** _____

#3 TLDA testing of bone marrow for neuroblastoma tumor cells:

Researchers would like to take about 2 teaspoons (10 cc) of blood each time you have a routine bone marrow test done to check the response of the tumor in the bone marrow to the IV fenretinide. The results of the TLDA test will be confidential and will not be made available to you or your treating physician.

THESE TESTS ARE STRICTLY VOLUNTARY. YOU MAY STILL PARTICIPATE IN THE STUDY EVEN IF YOU DO NOT AGREE TO THESE TESTS.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have extra bone marrow tested for tumor using TLDA test

_____ **NO**, I do not agree to extra bone marrow tested for tumor using TLDA test

Signature: _____ **Date:** _____

STATEMENT OF CONSENT

I have been given a copy of all pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Patient Name

Signature of Parent or Guardian

____/____/____
Date

Signature of Parent or Guardian

____/____/____
Date

Signature of Patient (If > 7 years old)

____/____/____
Date

SIGNATURE OF PHYSICIAN OR
Responsible Investigator

____/____/____
DATE

Signature of Witness

____/____/____
Date

Signature of Translator
(If applicable)

____/____/____
Date

CONSENT ADDENDUM #1

A blank box means the test is not done at that time point in the study.

Tests that will be done on this study.

STUDIES TO BE OBTAINED	Pre-Study	During Course 1	Prior Each Course	During All Treatment Courses	Other Courses	Off Protocol Therapy
History	X		X			X
Physical Exam (Ht, Wt, BSA, VS)	X	X	X	X		X
Performance Status	X		X			X
Blood and/or urine tests	X	Day 0, 6, 8, 13	X	Day 0, 6 (Course 2 and 6 only)		X
Vision testing	X			Every 5 courses if normal at entry, otherwise, before every course		
Heart test (echocardiogram/MUGA and EKG)	X					X
Head Imaging (CT/MRI)	X					
CXR	X					
Tumor Imaging with CT/MRI and MIBG scans	X		Before Course 3 then every 4 courses.			X
Urine test (VMA/HVA)	X		Before Course 3 & 5 then every 4 courses.			X
Bilateral bone marrow aspirate and biopsy for routine morphology	X		Before Course 3 then every 4 courses.			X
Fenretinide Blood levels (REQUIRED)		Day 0, 6, 8		Day 0, 6 (Course 2 and 6 only)†		
Tests below this line would only be done if you gave permission for them to be done.						
TLDA test of bone marrow for tumor cells	X		After Course 2 and 6, and then every 4 courses if there was tumor seen in the bone marrow at study entry			
Fenretinide levels in normal white blood cells (OPTIONAL)				(D0, 6) Course 2 Only)		

†If your fenretinide or ketoconazole dose is changed, or you stay on study longer than 6 courses, you may be asked for fenretinide levels an extra time.

CONSENT ADDENDUM #2

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

16.0 SAMPLE ASSENT TO PARTICIPATE IN A RESEARCH STUDY

Using Fenretinide/LXS Oral Powder to Treat Patients with Recurrent or Resistant Neuroblastoma

Subject's Name:	_____	
Hospital#:	_____	Birth Date: _____

1. My name is _____.
2. You have a kind of cancer called **neuroblastoma**, which has either come back, or not gone away with the treatments you have already had. In the past, Doctors have found that giving a drug called **Fenretinide** by mouth may help to treat children with neuroblastoma like yours. In the past Fenretinide has only been available as large pills that can be very difficult to swallow (especially for small children). This study will use another form of Fenretinide (called "Fenretinide/LXS oral powder") that can be given by mouth. It will be given three times a day for seven days, every three weeks. It is also hoped that this way of giving Fenretinide might mean that patients taking it absorb (soak up) more of the Fenretinide. We are asking you take part in this research study because we are trying to learn more about what effects (both good and bad) a research treatment using the fenretinide/LXS oral powder has on patients with neuroblastoma.

You may also be asked to take a second drug, called Ketoconazole, along with the Fenretinide powder. Ketoconazole is a common antifungal drug used to treat toe nail fungus. We are testing to see if Ketoconazole can slow down how quickly that your body gets rid of Fenretinide. This might keep more Fenretinide in your body to fight the neuroblastoma.

3. If you agree to be in this study this is what will happen:

Coming to see the Doctor: You will need to come and see the doctor frequently while you are receiving the Fenretinide/LXS oral powder and maybe the Ketoconazole drug. Tests will be done before, during and after the time when you receive the Fenretinide/LXS oral powder. These tests include;

- Looking in your ears, eyes, listening to your lungs, heart and stomach – this is called a Physical Exam.
- Blood and urine tests.
- Test your heart and eyes.
- Scans (like MRI, MIBG, and CT scans).
- An X-Ray of your chest before you start the Fenretinide.
- Bone Marrow tests – you will have had these before as part of your treatment for your neuroblastoma.

Asking Questions: It is very important that you ask any questions you might have. Your Doctors, Nurses and all the people that work with you here at the Hospital will always try to answer your questions. If they don't know the answer, they will find someone who does.

Taking Fenretinide: You will be given Fenretinide/LXS oral powder, maybe with Ketoconazole, and take it in foods or beverages at home three times a day for seven days straight every three weeks. Some doses will need to be given in the outpatient clinic. This block of three weeks is called a **cycle**.

Blood Samples: Because we want to learn how well Fenretinide/LXS oral powder works, and how well your body absorbs (or soaks up) the Fenretinide we will need to take blood samples from you. These samples will be collected during the first, second, and sixth cycles of treatment. It is possible that we may need to change the dose of your Fenretinide or Ketoconazole, or that you may stay on the treatment for a long time. If you do, we may ask to check the fenretinide levels an extra time. If you do not have a central line you will have to have an i.v. started or be poked with a needle in your arm or hand. We can use numbing cream or “cold spray” so it doesn't hurt. The blood samples we just talked about are **required** – you must do them to be on the study.

There are also two other **optional** blood samples that you can choose to do or not. If you agree, we will take two extra blood samples on the 1st and 7th days of your second cycle of Fenretinide/LXS oral powder. These are fairly large samples (about 4 teaspoons each time). This would only be done if you were well enough and big enough to have the blood taken without hurting your body. You do not have to do this part of the study if you don't want to.

4. Sometimes things happen to children in research studies that may make them feel bad. These are called “risks”. The risks of this study are:
 - Dry skin, or a rash.
 - Your skin could be more sensitive to getting sunburned.

- Dry or irritated eyes.
 - Problems seeing when it is dark when you're getting the medicine and for a few days afterward – it is very important that if you are worried that you cannot see properly that you tell your Mom and Dad.
 - Swollen joints, sore joints or muscles.
 - Headache, dizziness or feeling lightheaded. It is very important that you tell your Mom and Dad when you have a headache.
 - Nausea, vomiting, tummy pain, tummy cramping or diarrhea (loose stools).
 - Increased pressure in your brain which may cause headache, vomiting or double vision.
 - You might have an allergic reaction to the Fenretinide.
 - **Risks from starting an IV and taking blood samples:** This can be painful. Sometimes you can get an infection or a blood clot in the IV so that the IV stops working and would need to be taken out and restarted in another place. Doctors or nurses who have started IV's many times will start your IV and take the blood samples.
 - Low number of red blood cells which may cause you to feel tired.
 - Low number of white blood cells which may lead to infection
 - Low number of platelets which may cause you to bleed more easily.
 - Higher amounts of a chemical called calcium in your blood (calcium is also in milk).
 - Low amount of a protein in your blood called albumin
 - Low amount of a chemical called phosphorous in your blood
 - Some fluid could build up around your lungs for a while.
 - Your kidneys may not filter your blood as well as they normally do for a while.
 - You could have strange dreams.
 - You could have lots of farting (passing gas).
 - You could have hard stools (constipation).
 - Your liver could be badly damaged from the medicines.
5. People also have good things that happen to them when they are in research studies. These are called "benefits". This treatment may help your neuroblastoma but you shouldn't think that your neuroblastoma will completely go away if you take part in this study. We hope to learn more about this treatment that will help other kids like you with neuroblastoma.
6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to you.
8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me, or ask me next time.

Optional Blood Samples

Please check to show if you do or do not agree to allow us to take the two extra blood samples.

_____ Yes, it is okay to take the extra two blood samples.

_____ No, it is not okay to take the extra 2 blood samples

9. Signing your name on the next page means that you agree to be in this study. Your doctors will continue to treat you whether or not you participate in this study. You and your parents will be given a copy of this form after you have signed it.

Name and Signature of Subject

Date

Signature of Investigator

Date

